Modelling the effects of continuous irradiation on murine haematopoiesis

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Abstract. During continuous irradiation of mice, several effects on the haematopoietic system are observed. Haematopoiesis is able to maintain a stable, steady state for many weeks if daily doses do not exceed 0.6–1 Gy day $^{-1}$. The steady state is characterized by a sustained marked reduction of the haematopoietic stem cells measured by the spleen colony-forming unit assay, while erythropoietic and granulopoietic precursor cells are much less reduced. Daily doses exceeding 1 Gy day $^{-1}$ lead to a breakdown of haematopoiesis. These observations are analysed using a mathematical model of stem cell regulation. The analysis suggests that the relative radiosensitivity of stem cells under continuous irradiation is approximately 50% higher than for more differentiated cells. Doses above 0.25 Gy day^{-1} cause a peripheral demand for erythrocytes and granulocytes, which has an indirect radioprotective effect on the marrow cell compartments owing to feedback regulation.

The influence of continuous irradiation on haemopoietic stem cells in mice has been extensively examined experimentally [1–18]. Animals were exposed to daily doses between 0.01 Gy day $^{-1}$ and 10 Gy day $^{-1}$, and changes in the number of spleen colony-forming units (CFU-S) were investigated [9].

Typically, time courses are biphasic. After an initial decrease lasting several days, numbers of CFU-S level off at an equilibrium cell number significantly below the normal value. Both the rate of decrease and the plateau of the steady state are dose dependent. For doses above 0.6–1 Gy day $^{-1}$, the system continuously declines and finally fails.

Less is known about the behaviour of more mature cell stages during continuous irradiation. No data are available for erythrocyte blast-forming units (BFU-E), and there are little data for granulocyte-macrophage colony-forming units (CFU-GM) [10, 16], erythrocyte colony-forming units (CFU-E) [16] and erythroid responsive cells (ERC) [11]. Iron uptake has been measured only once in mice [14] and once in rats [1]. Total nucleated cell counts, however, have been recorded several times [7, 13, 15, 17, 19]. Information on granulopoietic and erythropoietic precursors is found in only one reference [3]. In general, the differentiated bone marrow cells show a higher plateau than has been observed for stem cells at the same radiation dose. This can even lead to the paradox that the levels of precursors remain almost normal while the CFU-S are already reduced to 20% [1, 7, 12, 14].

Peripheral blood counts have been repeatedly examined during continuous irradiation [7, 10, 14, 18–20]. Up to a dose of 0.25 Gy day $^{-1}$ the erythrocyte count will not drop below 85% of the normal value [10, 18–20]. For higher doses, the red cell count may drop to lower values in a dose-dependent manner [7, 10, 14, 19]. Blood granulocyte counts appear to be more sensitive to continuous irradiation. They show a clear reduction by at least 30% at doses as low as 0.1 Gy day $^{-1}$ [18–20]. Values below 25% of normal are reached if daily radiation doses exceed 0.25 Gy day $^{-1}$ [7, 10].

Mathematical methods

The experiments on continuous irradiation are simulated by an established mathematical model of stem cell regulation [21–23]. For this simulation and for the comparison with experimental doses, one must determine:

1. How to describe the continuous destruction of cells in mathematical terms.
2. How to consider the different radiosensitivities of various cells types.
3. How to relate the mathematical parameters to experimental doses.
4. How to consider the peripheral stimuli owing to anaemia and neutropenia.
5. How to identify the "limiting dose" beyond which haematopoiesis fails to maintain a steady state.

These points are considered in the following sections.

Modelling the continuous destruction of cells by radiation damage

To model the specific effect of continuous destruction due to radiation damage, it is assumed that the cells in each compartment are destroyed "at random", *i.e.* irrespective of the cell cycle stage of individual cells. Compartment contents are reduced as a proportion of their numbers, and the loss coefficients representing destruction are considered to be constant with time. To describe haematopoietic cell production from the stem cells to progenitor cells in the bone marrow, six cell compartments are considered: (i) the common bipotent erythropoietic/granulopoietic stem cells (S), to be compared with CFU-S; (ii) the erythropoietic burst-forming cells (BE), to be compared with BFU-E; (iii) the erythropoietic colony-forming cells (CE), to be compared with CFU-E; (iv) the erythroid precursor cells (E), to be compared with erythroblasts; (v) the granulopoietic colony-forming cells (CG), to be compared with CFU-GM; and (vi) the granuloid precursor cells (G), to be compared with all myeloblasts and granulocytes in the bone marrow. We describe the changes in these compartments using differential equations with random transition terms. Cell production is considered to be a multiplicative factor acting on the input term in each equation. For example, the input into cell compartment CE (CE^{in}) is obtained by the efflux of the preceding cell stage BE multiplied by an amplification factor Z_{CE}, which takes into account the cell production in cell stage CE. It should be noted that these amplification factors are assumed to be dependent on erythropoietin (EP) for CE and E, and on G-CSF for G. This allows regulation of demand from the peripheral cell stages to the bone marrow cells. Mathematically, this leads to the following equations [22]:

$$\frac{d}{dt}S = (2p-1)S \times \frac{a}{\tau_S} - K_S \times S \qquad (1)$$

$$\frac{d}{dt}BE = BE^{in} - \frac{BE}{T_{BE}} - K_D \times BE \qquad (2)$$

$$\frac{d}{dt}CE = CE^{in} - \frac{CE}{T_{CE}} - K_D \times CE \qquad (3)$$

$$\frac{d}{dt}E = E^{in} - \frac{E}{T_E} - K_D \times E \qquad (4)$$

$$\frac{d}{dt}CG = CG^{in} - \frac{CG}{T_{CG}} - K_D \times CG \qquad (5)$$

$$\frac{d}{dt}G = G^{in} - \frac{G}{T_G} - K_D \times G \qquad (6)$$

where τ_S is the cell cycle time and T_i are time constants.

Varying radiosensitivities of different cell types

Since not enough data are available to estimate the loss coefficients for the different cell compartments separately, only two loss coefficients are considered, one for the stem cells (K_S) and one for the differentiated cells (K_D). Thus, it is assumed that all differentiated cells have a similar radiosensitivity, which is different to that of the stem cells. The mathematical relationship between K_D and K_S must be determined from the data.

Relating mathematical parameters to experimental doses

The relationship between the experimental dose and the loss coefficients of the model must be identified. For this purpose, measurements between day 30 and day 45 of continuous irradiation are taken as steady-state values and are related to the experimental doses. In a similar way, the calculated steady-state values (taken on day 40) are related to the loss coefficients. It is then possible to match the experimental dose–response curve to the model dose–response curve by an appropriate choice of scaling factors so that they can be drawn on the same diagram. These scaling factors represent the relationship between the experimental doses and the loss coefficients of the model. Chronic destruction of immature haematopoietic cells leads to anaemia and neutropenia in the peripheral blood. The resulting need for mature cells stimulates amplification of erythropoietic and granulopoietic precursors (via EP and G-CSF) and thus indirectly influences intramedullary feedback. Blood granulocytes are more severely reduced than erythrocytes, but for granulopoiesis it is the total pool of granulocytes (in the bone marrow and the blood) rather than blood granulocytes alone that are responsible for feedback in the model [24–27]. Total granulocytes show a similar behaviour to erythrocytes under continuous irradiation [24, 25]. Therefore, in the model it is assumed that the demand for erythropoietic and granulopoietic cells increases in parallel. Consequently, E and G, as well as BE and CG, will behave very similarly. In the model, the similarity of granulopoietic and erythropoietic stimulation is simulated by calculating only erythropoiesis and assuming that the granulopoietic progenitors and precursors show the same behaviour as their erythropoietic counterparts (CG = BE; G = E).

Consequently, the regulatory functions p and a governing the stem cell compartment depend only on the status of the stem cell compartment and the erythroid/granuloid precursors:

$$p = p(S,E) \text{ and } a = a(S,E) \qquad (7)$$

The function p, called the self-renewal fraction, determines whether the stem cell compartment increases or decreases. The regulatory effects act as follows: a reduction of S leads to an increase of p, while a reduction of E leads to a decrease of p. If both cell compartments are reduced, the relative weight of S overrules the weight of E to ensure self-renewal. The function a determines the proliferative fraction and hence the cell turnover. Any reduction in S or E will activate stem cells into proliferation and thereby enhance cell output to replenish

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Table 1. Dose–response relationships predicted by the model for haematocrit (Hct) and erythropoietin (EP) developing during the plateau phase of continuous irradiation (day 40)

Dose (Gy day)	0.03	0.1	0.25	0.5	0.7
Loss coefficient K_S (h)	0.0011	0.0035	0.0088	0.0175	0.0245
Hct (× normal value)	0.99	0.98	0.92	0.72	0.38
EP[a] (× normal value)	1.03	1.12	1.43	4.75	200.0

[a]EP values have been determined from Hct using a model of mature erythropoiesis [28, 29].

the precursor pools.

The above model of stem cell haematopoiesis needs to be supplemented by a model of mature erythropoiesis to account for the stimulation of erythropoiesis exerted by EP owing to anaemia developing under continuous irradiation. Details of how this can be performed can be found elsewhere [28, 29].

The increase in EP is a consequence of the hampered production of red blood cells resulting from irradiation, demonstrating the anaemic stimulation that develops [29]. Table 1 gives some examples of the dose dependence of EP levels predicted to occur under continuous irradiation. Minor changes of haematocrit and EP are found up to 0.25 Gy day $^{-1}$. For higher doses the anaemic stimulus increases dramatically.

The chronic destruction of cells leads to a subnormal plateau of cell numbers both in the experiments and in the model. The plateau depends on the dose and will be lower at higher doses. However, there exists a threshold beyond which no plateau is reched and the animal dies. Experimentally, this "limiting dosage" can be measured. In the model, it can be calculated from the steady-state condition. Equation (1) gives the relation:

$$(2p - 1)a/\tau_S = K_S \qquad (8)$$

The maximum values for a and p are 1.0 and 0.6 [22]. With the cell cycle time $\tau_S = 8$ h, one finds the limiting loss coefficient $K_S = 0.025$ h $^{-1}$. Higher values lead to failure of the system.

In the following, a steady-state analysis of the experimental data in the plateau phase of continuous irradiation will be performed first. This analysis leads to an estimate of the scaling factors between the experimental dose and the loss coefficients for stem cells (K_S) and differentiated cells (K_D). From these factors, the relative radiosensitivity of the cells can be derived and the theoretical dose limit can be expressed in Gy day $^{-1}$. Furthermore, the contribution of amplifying divisions (stimulated by EP) can be quantified.

With the knowledge obtained from the steady-state analysis, the system dynamics in non-steady state are then investigated. A number of experimentally relevant doses will be simulated and the critical region close to the limiting dose will be analysed.

Results

Steady-state analysis

From the plateau values of the available data [2, 3, 7, 9–11, 13, 14, 17–20] between day 30 and day 45, the following information can be derived.

Dose–response relationship of stem cells

In the model, the severity of continuous irradiation is quantified by loss coefficients. K_S is the parameter for fractional loss of stem cells per hour. The experimental dose is usually measured in Gy day $^{-1}$. A good match of model dose–response (for S) with experimental dose–response (for CFU-S) can be achieved with a scaling factor of 0.035 [day (Gy × h) $^{-1}$], as shown in Figure 1a:

$$K_S\ (\text{h}^{-1}) = 0.035 \times \text{dose (Gy day}^{-1}) \qquad (9)$$

This relationship defines how a certain value of K_S can be derived for a given dose. We use Equation (9) in all three dose–response relations (Figures 1a–c) as the gauge for the axes.

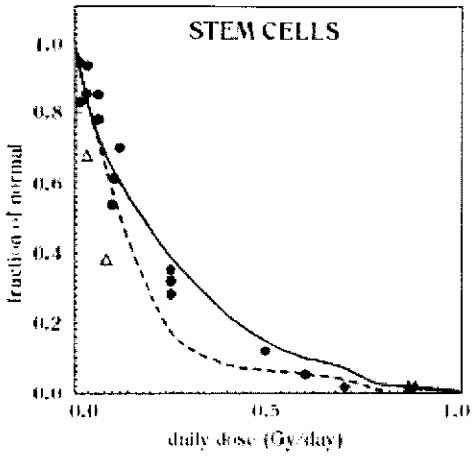
Dose–response relationship of differentiated cells

Similarly, one can match the plateau values for progenitors and precursors from the model with the experimental values (Figure 1b). K_D is the parameter for the fractional loss of differentiated cells per hour. The same value of K_D is taken for all progenitors and precursors. A good match is obtained if K_D is evaluated for a given dose with a scaling factor of 0.023 [day (Gy × h) $^{-1}$]:

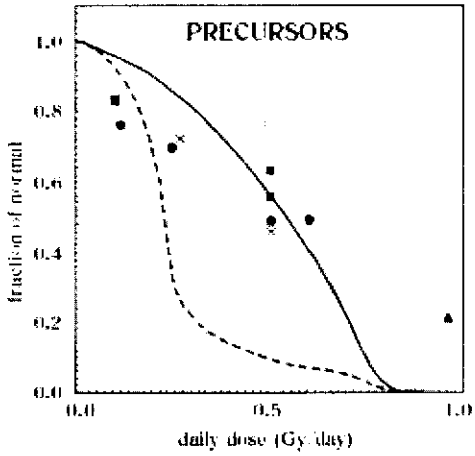
$$K_D\ (\text{h}^{-1}) = 0.023 \times \text{dose (Gy day}^{-1}) \qquad (10)$$

Radiosensitivity

The scaling factors in Equations (9) and (10) have been obtained by matching the model results in steady state with the corresponding data points (Figures 1a and 1b). Obviously, this is a crude method based on simplification of a linear relationship between loss coefficients and dose and an identical radiosensitivity of all differentiated cells. The equations suggest that for an



(a)



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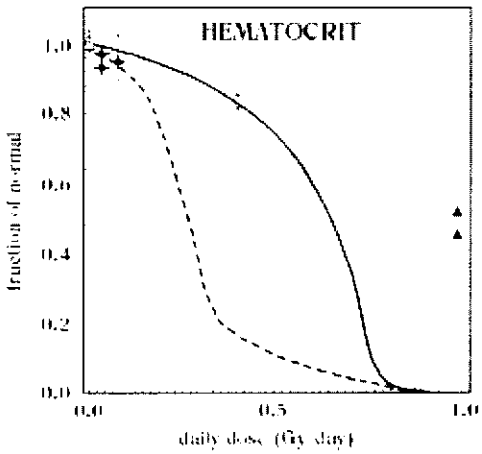

(c)

Figure 1. Relationship between daily dose of continuous irradiation and the plateau values of (a) stem cells (spleen colony-forming units (CFU-S)), (b) precursor cells and (c) haematocrit. Model curves correspond to day 40 of simulated continuous irradiation. The solid line takes into consideration peripheral stimulation and represents the dose–response curve of the model including all levels of feedback regulation. The dashed line shows the hypothetical situation of no peripheral stimulation. On the abscissa, 1 Gy day^{-1} corresponds to a loss coefficient K_S of 0.035 h^{-1}. (**a**) Experimental points (CFU-S [2, 7, 9–11]) have been derived between day 30 and day 45 of irradiation. Data taken from: ●, Kalina et al [6]; ▲, Kalina et al [7]; Δ, Drasil et al [2]; ♦, Lajtha et al [11]; ○, Knospe et al [10]. (**b**) Data taken from: total erythroblasts: □, Fedotova and Belousova [3]; total myeloblasts: ■, Fedotova and Belousova [3]; total nucleated cells: ●, Kalina et al [6]; ▲, Kalina et al [7]; ×, Muskinova [17]. (**c**) Data taken from: +, Lorenz et al [19]; ○, Knospe et al [10]; ▲, Kalina et al [7]; ◊, Praslicka and Kalina [18]; ★, Spargo et al [20]; *, Twentyman and Blackett [14].

increase in dose of 0.1 Gy day^{-1}, an additional 0.35% of stem cells and 0.23% of differentiated cells are destroyed per hour in each compartment.

The ratio r of the scaling factors (and thus the ratio K_D:K_S) can be interpreted as the relative radiosensitivity of differentiated cells compared with stem cells and shall be denoted by:

$$r = K_D/K_S \qquad (11)$$

Here one finds r = 0.66, suggesting that the differentiated cells are two-thirds as radiosensitive to continuous irradiation as stem cells, *i.e.* stem cells are 50% more radiosensitive.

Influence of peripheral stimuli

During continuous irradiation, anaemia develops. The data points in Figure 1c indicate to what degree the haematocrit has fallen between day 30 and day 45 [7, 10, 14, 18–20]. In the model, a similar reduction is found (solid line): the curve is derived from values at day 40 of simulated continuous irradiation. The (solid) dose–response curve in Figure 1c corresponds to the (solid) curves in Figures 1a and 1b. In these curves, peripheral stimulation is considered. It is interesting to ask what the dose–response curves would look like if peripheral stimulation via EP and G-CSF was not effective. This is shown by the dashed lines in Figures 1a–c. The comparison of solid and dashed lines shows that the amplifying divisions, which are induced by peripheral stimulation, increase the number of precursors (Figure 1b) and, subsequently, the haematocrit (Figure 1c). The higher number of precursors has a beneficial effect on stem cell numbers, which are also kept at a higher level (Figure 1a). The latter is an indirect consequence of intramedullary feedback and is not as pronounced as the direct stimulatory effect on the precursors.

Limiting dose

From Equation (9) it can be concluded that the haemopoietic system, as simulated by the model, fails when the loss coefficient K_S exceeds 0.025 h^{-1}. Using Equation (9), this leads to a limiting dose of 0.71 Gy day^{-1}. For higher doses in the model, no steady state can be reached. Experimentally, one finds the limiting dose to be between 0.6 Gy day^{-1} and 1 Gy day^{-1} [6, 11, 15, 16].

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Dynamic behaviour

Model calculations

Using the relationships between loss coefficients and dose, the time course of the changes in cell numbers during continuous irradiation can now be simulated. This has been done for five different doses (0.03 Gy day $^{-1}$, 0.1 Gy day $^{-1}$, 0.25 Gy day $^{-1}$, 0.5 Gy day $^{-1}$ and 0.7 Gy day $^{-1}$) and is shown in Figures 2a–d.

Depending on the dose, anaemia (and neutropenia) of increasing severity develops. Accordingly, EP levels increase in the erythropoiesis model in a dose-dependent manner (Figure 2a). These EP curves are used as input to the model. During continuous irradiation, S decreases for several days and, after some minor fluctuations, tends towards a new steady state. Both the rate of decrease and the steady-state level are dose dependent (Figure 2a). A similar behaviour is found for BE and CG. However, the curves are slightly higher than for S, with E and G exhibiting a more interesting pattern (Figure 2b). For low doses below 0.4 Gy day $^{-1}$ these compartments show steady-state values close to normal. For higher doses, their steady-state values are reduced but remain above those of S.

The behaviour of the stem cells can be understood as follows. Owing to the constant removal of cells, S is reduced and the self-renewal probability p (Figure 2c) as well as the proliferative fraction a (Figure 2d) increase. Thus, more new stem cells are produced. In the first days this gain is insufficient to compensate for the loss due to irradiation. Only after several weeks does the system adapt and a balance between loss and gain is achieved.

The behaviour of BE, CG and CE is mainly determined by increases in the proliferative fraction. The increase in a (Figure 2d) maintains CE at almost normal levels for low doses where EP is barely elevated. For higher doses (above 0.3 Gy day $^{-1}$) the increased production of stem cells alone can no longer maintain these high precursor cell counts. Up to two additional amplifying divisions at the precursor stage are then activated by peripheral stimulation. This keeps the precursor cells and, consequently, the erythrocytes and granulocytes, at relatively high levels.

Comparison with data

Figures 3a–f provide data for continuous irradiation with doses between 0.03 Gy day $^{-1}$ and 0.7 Gy day $^{-1}$. They can be compared with the model curves in Figures 2a–d.

Many measurements of CFU-S are available, only some of which are reproduced here (Figure 3a). CFU-S show the same biphasic behaviour as the S curves. At comparable doses, the steady-state values for CFU-S and S are similar. However, during the initial phase the calculated S curves drop faster than the corresponding CFU-S curves.

Information regarding the behaviour of the progenitors CFU-GM and CFU-E (Figures 3b and 3d) is scarce. CFU-GM fit the model curves well, while CFU-E remain below the corresponding calculations. No measurements are available for BFU-E.

The data on erythropoietic, granulopoietic and total nucleated precursors [1, 3, 7, 11, 13, 15–18] show that the cell numbers do not differ very much from normal at doses below 0.5 Gy day $^{-1}$ (Figures 3c, 3e and 3f). Characteristically, all values are higher than the corresponding stem cell values at the same dose.

Limiting dose

In Figures 2a–d, loss coefficients have been considered that correspond to doses between 0.03 Gy day $^{-1}$ and 0.7 Gy day $^{-1}$. In these figures, higher doses lead to lower plateaus. However, there is a critical dose for which no subnormal steady state exists and where the cell numbers decrease to zero. In the model, this critical dose corresponds to 0.71 Gy day $^{-1}$ or, in model terms, to $K_s = 0.025$ h $^{-1}$. For higher doses a steady state becomes impossible because the loss of stem cells is permanently greater than the maximum gain of new stem cells. Figures 4a–c show the behaviour of the system near this threshold value. At 0.7 Gy day $^{-1}$, a steady state is still achieved in S, while at 0.75 Gy day^{-1} a monotonous decline is found, which is even more pronounced at 0.8 Gy day $^{-1}$.

A similar behaviour is found for the experimental cell numbers, although here the border between survival and death cannot be drawn so precisely as in the model. Nevertheless, for doses between 0.6 Gy day $^{-1}$ and 1.0 Gy day $^{-1}$, CFU-S continuously decline [2, 3, 6–9, 11, 12] and eventually die out.

Discussion

As has been demonstrated, the mathematical model of stem cell regulation is able to provide an explanation for the behaviour of haemopoietic bone marrow cells during continuous irradiation. The model helps to establish a rough estimate for radiosensitivity of cells, showing that in the experiments stem cells are approximately 50% more radiosensitive to continuous irradiation than differentiated cells. This result is surprising because the dose–response curves (Figures 1a and 1b) would suggest a much greater difference. However, it can be understood if one considers the regulatory influence of functional cells on granulopoietic and erythropoietic precursors. The peripheral demand induces additional mitoses in the precursor stages. The higher numbers of precursors reduces the differentiation pressure on the stem cells and thus the stem cell pool is less depleted. In total, one finds an indirect radioprotective effect of peripheral stimulation on both stem cells and precursor cells.

Mathematically, the influence of blood cells has been simulated in a simplified way. As the stem cell model discussed here lacked a description of mature granulocyte and erythrocyte formation, information regarding

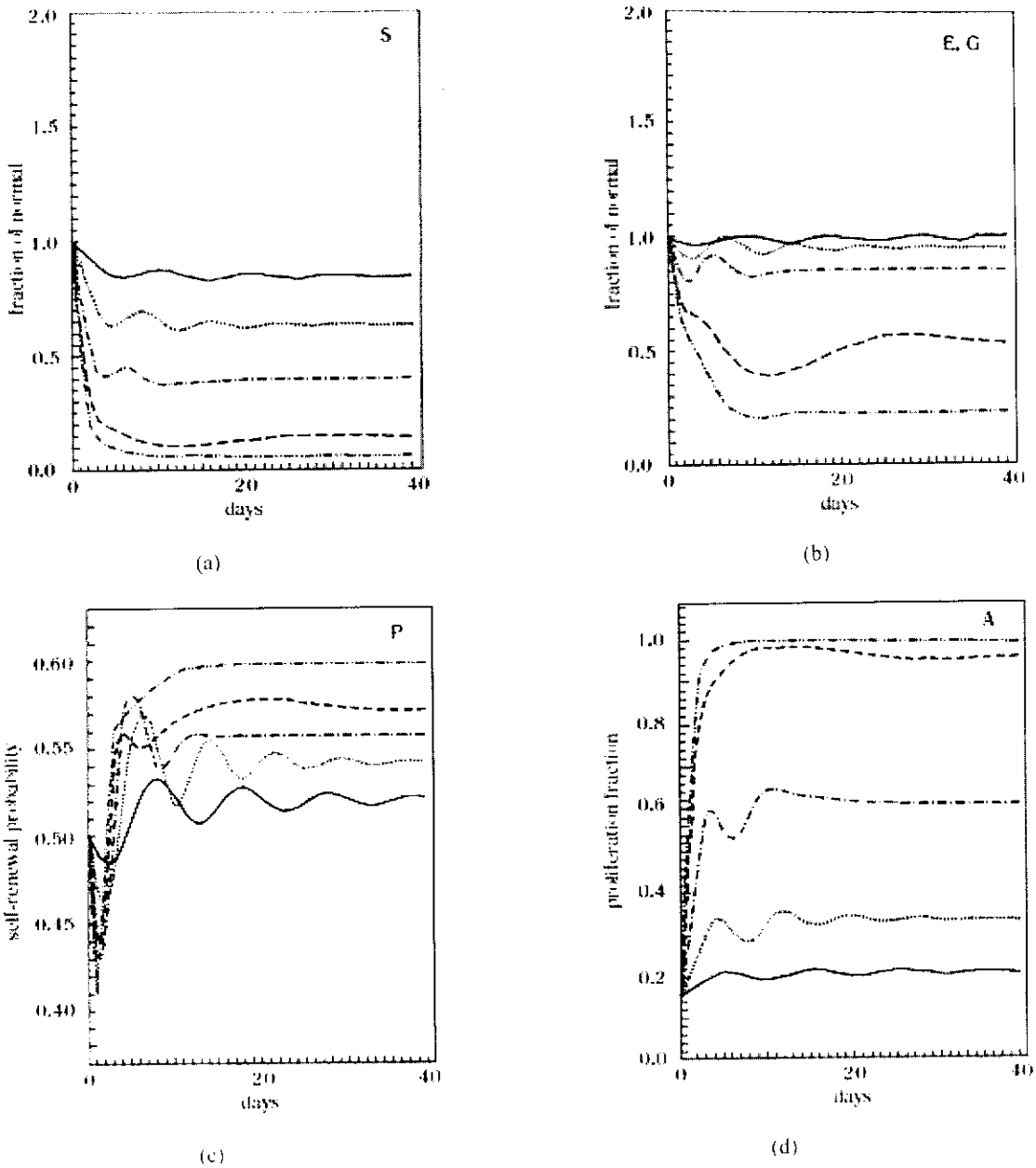

Figure 2. (a–d) Model simulation of the time course of continuous irradiation. The simulation corresponds to five different doses: 0.03 Gy day^{-1} (— —); 0.10 Gy day^{-1} (·····); 0.25 Gy day^{-1} (–·–·–·–); 0.50 Gy day^{-1} (– – – –); and 0.70 Gy day^{-1} (–··–··–··–). The model curves for BE and CG, and those for E and G, are identical. Anaemia that develops during continuous irradiation is considered using the theoretical values for erythropoietin (EP) shown in Table 1. These EP values are used as input for the model.

erythropoietic and granulopoietic stimulation during continuous irradiation had to be taken from different sources. Applying an established model of mature erythropoiesis [28, 30] allows the EP values to be calculated from the observed degree of anaemia. These values are then introduced into the stem cell model. For granulopoiesis we have assumed that it follows the same characteristics as erythropoiesis. This is the simplest assumption without introducing additional model parameters.

The finding that anaemia and neutropenia have a protective effect on stem cell numbers during continuous irradiation is perhaps surprising. However, it is biologically reasonable. From the model point of view, it is important to note that this "self-protection" is not an additional assumption, but is a consequence of our description of intramedullary feedback, in which an increase of the precursors indirectly leads to an increase of the stem cells.

It is obvious that the relationship between loss coefficients and experimental doses can only be a rough measure because the use of constant coefficients is a simplification that neglects important biological mechanisms, for example consideration of repair mechanisms would lead to lower loss coefficients in the beginning (repair) and higher values in later phases (residual damage). Such a model description would be biologically more reasonable, but there is not enough

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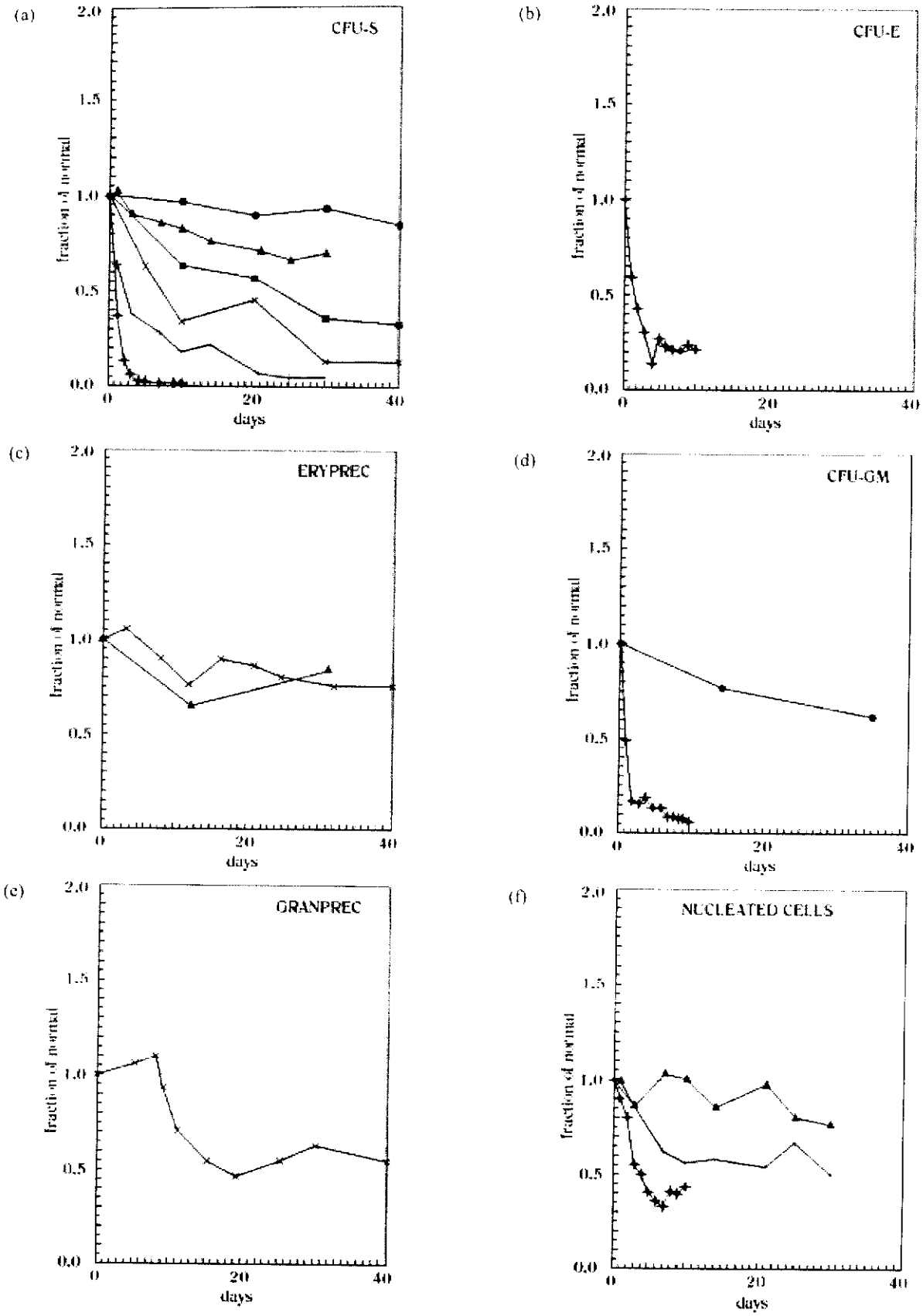
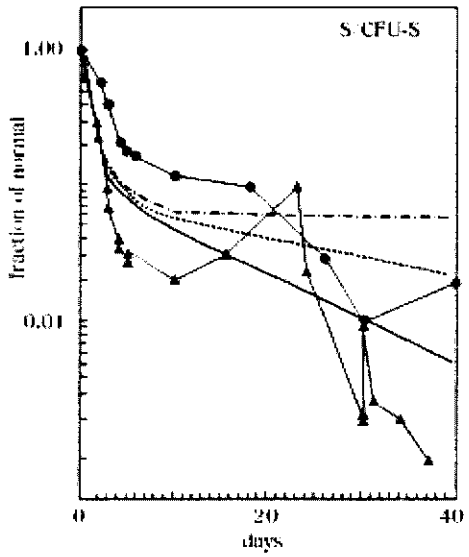
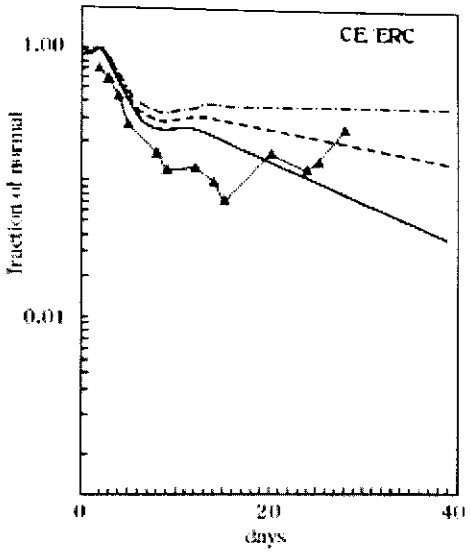


Figure 3. (a–f) Cell numbers measured in the bone marrow of mice during continuous irradiation. The symbols represent the daily dose ranges: ■, 0–0.05 Gy day^{-1}; ●, 0.06–0.15 Gy day^{-1}; ▲, 0.16–0.45 Gy day^{-1}; ×, 0.46–0.55 Gy day^{-1}; +, 0.56–0.65 Gy day^{-1}; ★, 0.66–0.75 Gy day^{-1}. Data taken from: CFU-S: Kalina [9], 0.03 Gy day^{-1}, 0.11 Gy day^{-1}, 0.25 Gy day^{-1}, 0.5 Gy day^{-1}, 0.6 Gy day^{-1}; Wu et al [16], 0.7 Gy day^{-1}. Erythropoietic precursors: Fedotova and Belusova [3], 0.1 Gy day^{-1}, 0.5 Gy day^{-1}. CFU-GM: Knospe et al [10], 0.25 Gy day^{-1}; Wu et al [16], 0.7 Gy day^{-1}. Granulopoietic precursors: Fedotova and Belousova [3], 0.5 Gy day^{-1}. Total nucleated cells: Kalina [9], 0.11 Gy day^{-1}, 0.6 Gy day^{-1}, 1.0 Gy day^{-1}; Wu and Lajtha [15], 0.7 Gy day^{-1}.



(a)



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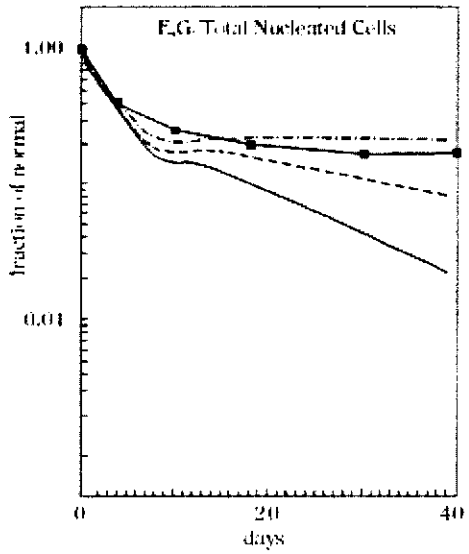

(c)

Figure 4. (a–c) Model behaviour during continuous irradiation near the limiting dose of 0.71 Gy day^{-1} (for higher doses the system fails). The figures show three model calculations at 0.70 Gy day^{-1} (.....), 0.75 Gy day^{-1} (- - -) and 0.80 Gy day^{-1} (—). Only in the first case is a steady state achieved. In the other two cases stem cell numbers decrease steadily. Data are shown for comparison. CFU-S and ERC: ▲, Lajtha et al [11], 0.7 Gy day^{-1}. CFU-S: ●, Kalina et al [7], 1.0 Gy day^{-1}. Total nucleated cells: ■, Kalina [9], 1.0 Gy day^{-1}.

information available to quantify these effects. Furthermore, quantitative differences in the relationship between loss coefficients and doses may occur for different mouse strains and radiation sources from those used in the experiments analysed here.

It should be noted that similar kinds of modelling have been performed for continuous exposure with toxic agents such as benzene and benzoapyrene [31, 32]. They also showed that rather substantial daily losses of cells owing to toxic effects can be compensated for by the haematopoietic system.

The general model-based findings are that cell numbers in the peripheral blood or differentiated cell numbers in the bone marrow can appear rather unperturbed and close to normal while the system is suffering rather marked damage. It is crucial to investigate the status of the haematopoietic stem cells as the most sensitive cell stage to obtain an adequate insight into the effects of continuous irradiation. The ability of the system to counteract damages inflicted on it is certainly remarkable but also invalidates measures of effect using the level of peristerol cell counts. All effects imposed are counteracted by regulatory processes. This is the major reason for dynamic modelling as it provides a possibility to segregate effects of damage and compensatory regulatory processes.

The above work was performed in the mid 1980s on the murine system. In the meantime there have been two developments that will enable further progress. First, we have been able to design similar models for human haematopoiesis. A model for granulocytopoiesis has been developed that is presently in use to describe the effects of cytostatic chemotherapy and G-CSF application to optimize cancer treatment protocols [26, 27]. This model

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will now be used to evaluate the effects of chronic and acute radiation hazards on humans.

A second development concerns the concept of haematopoietic stem cells. The concept has been criticized as ignoring stem cell subpopulations that are not all self-renewing. We have recently proposed a novel class of haematopoietic stem cell models that take into account stem cell plasticity in the sense that subpopulations can be generated in reversible ways if specific microenvironmental restrictions are imposed. This type of model is able to reconcile a large variety of experimental findings on clonal development, on cell kinetic properties and on cell–microenvironment interactions [33, 34]. An analysis is underway to examine how the effects of continuous irradiation can be incorporated into this novel model. Preliminary results, however, support the above conclusions that continuous irradiation primarily damages the stem cell pool and thereby leads to activation of cell kinetics and a more pronounced turn over.

Acknowledgment

This paper is a revised version of a previous publication [35].

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